Strategies to develop putative biomarkers to characterize the female phenotype with autism spectrum disorders

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Torres EB, Isenhower RW, Yanovich P, Rehrig G, Stigler K, Nurnberger J, José JV. Strategies to develop putative biomarkers to characterize the female phenotype with autism spectrum disorders. J Neurophysiol 110: 1646–1662, 2013. First published July 17, 2013; doi:10.1152/jn.00059.2013.—Current observational inventories used to diagnose autism spectrum disorders (ASD) apply similar criteria to females and males alike, despite developmental differences between the sexes. Recent work investigating the chronology of diagnosis in ASD has raised the concern that females run the risk of receiving a delayed diagnosis, potentially missing a window of opportunity for early intervention. Here, we retake this issue in the context of the objective measurements of natural behaviors that involve decision-making processes. Within this context, we quantified movement variability in typically developing (TD) individuals and those diagnosed with ASD across different ages. We extracted the latencies of the decision movements and velocity-dependent parameters as the hand movements unfolded for two movement segments within the reach: movements intended toward the target and withdrawing movements that spontaneously, without instruction, occurred incidentally. The stochastic signatures of the movement decision latencies and the percent of time to maximum speed differed between males and females with ASD. This feature was also observed in the empirically estimated probability distributions of the maximum speed values, independent of limb size. Females with ASD showed different dispersion than males with ASD. The distinctions found for females with ASD were better appreciated compared with those of TD females. In light of these results, behavioral assessment of autistic traits in females should be performed relative to TD females to increase the chance of detection.

sex differences; autism; kinesthetic input; decision-making; movement decision time; stochastic signatures

The current diagnosis of autism spectrum disorder (ASD) (American Psychiatric Association 2000) does not make provisions to distinguish between males and females despite known developmental sex differences across a broad range of parameters, from physiological to cognitive milestones, including language. Typically developing (TD) boys are known to lag behind girls initially, but eventually, boys catch up (Stromswold 1998), and by adulthood, some complementary sex differences may emerge (Adam et al. 1999; Der and Deary 2006; Kaushanskaya et al. 2011), suggesting parallel learning paths.

In children who have already been diagnosed with ASD, girls—particularly those without marked cognitive impairments—may have been formally identified at a later age than boys, which may have impeded referral for early interventions (Giarelli et al. 2010). Because the diagnosis of ASD is centered on cognitive impairments [Autism Diagnostic Observation Schedule (ADOS) (Berument et al. 1999) and Gilliam Autism Rating Scale, Second Edition (GARS-2) (Campbell 2005; Lecavalier 2005)] and the observation that there is a large sex difference in the prevalence of ASD (~5:1 boys:girls) (Lord and Bishop 2010; Mandy et al. 2011; Newschaffer et al. 2007; Volkmar et al. 1993), it seems important to develop noninvasive tests on cognitive performance (e.g., decision-making tasks) that may be administered easily in a clinical setting to identify possible systematic sex differences across ages. This information would be extremely valuable given its implications for the correct standardization of sex-based cognitive metrics. Furthermore, sex differences in brain development have been used to anchor cognitive theories of ASD (Baron-Cohen 2002; Baron-Cohen et al. 2003) with support from subjectively self-reported surveys, inventories, and meta-analyses (Lai et al. 2011). At present, however, no operational definition has been provided that permits fast, automatic, and objective screening for sex differentiation in clinical settings. This is particularly so as the individual ages and his/her sensory-motor systems adapt to new developmental changes.

The traditional approaches to ASD research across all areas of cognition, perception, and action have focused, thus far, on disruptions of goal-directed and intentional aspects of behavior, assumed to be centrally driven. These include planning, coordination, and motor learning (Fournier et al. 2010a, b; Gidley Larson et al. 2008; Gowen et al. 2008; Haswell et al. 2009; Izawa et al. 2012; Jansiewicz et al. 2006; Jones and Prior 1985; Minshew et al. 2004; Mostofsky et al. 2006; Noterdaeme et al. 2002; Rinehart et al. 2001; Rogers et al. 1996; Williams et al. 2001), just to mention a few.

Behavior, however, flows continuously rather than as a discrete set of goal-directed segments. Although there is intentionality in much of what we do, the fluidity of our actions depends heavily on spontaneous segments “gluing” our goal-directed acts (Torres et al. 2011). Very little is known about the...
potential contributions of reflexive, spontaneous, and automatic reactions that without explicit awareness, co-occur in complex behaviors. Some of these types of motions are known to be disrupted in infants that go on to receive a diagnosis of ASD (Teitelbaum et al. 1998) and persist in excess (Mminderaa et al. 1985; Reed 2007) or are different in older children and adolescents with ASD (Torres 2013a; Torres et al. 2013a).

Spontaneous aspects of motor control also break down when subcortical structures are compromised in adults (Torres et al. 2011), and the endogenous feedback from the rotating arm joints breaks down. A large body of work from motor control (Redgrave and Coizet 2007; Redgrave et al. 2010; Shadmehr and Wise 2005; Smith et al. 2011) suggests that peripheral motor input and subcortical structures are important to develop a good balance between intended and automatic aspects of behavior. However, the body of work of movement neuroscience has yet to make contact with the field of autism. The research literature on autism focuses at present on cognitive and social issues, as if these were disconnected from movement and movement sensing.

In autism, a disorder diagnosed after 3 yr of age, the links and pathways between voluntary and automatic structures for central- and peripheral-based control may have developed differently. Problems with movement and movement sensing have been reported in ASD (Donnellan et al. 2012; Donnellan and Leary 2012; Savarese 2013). These problems could be quantified objectively at the motor output level to begin elucidating the various contributions of different aspects of motor planning and execution to these disturbances. We know that several of the cortical and subcortical structures that are targeted by general somatic afferent (GSA) fibers are reportedly impaired in ASD, along with anomalies involving central and peripheral synapses (Amaral and Corbett 2003; Amaral et al. 2008; Breece et al. 2012; Damasio and Maurer 1978; Jacobson et al. 1988; Maurer and Damasio 1979, 1982; Mostofsky et al. 2009; Nordahl et al. 2012; Qiu et al. 2010; Rinehart et al. 2002; Schumann et al. 2004; Takarai et al. 2007). Nevertheless, features of movement kinematics from the peripheral limbs are not well understood in ASD. It is not known if sex differences could be found in relation to such parameters.

Disturbances in the peripheral nervous systems (PNS), related to self-regulation, body autonomy, and volitional control, also abound in ASD. Some of these may impact movement and could be reflected in the continuous flow of motions, including the spontaneous segments of natural behaviors. Some of the well-known peripheral issues include problems with the autonomic nervous system, involving the enteric (gastro-intestinal) subsystems of the PNS (Ashwood et al. 2003; Buie et al. 2010; de Magistris et al. 2010; Kushak et al. 2011; MacFabe et al. 2011; Mazurek et al. 2013; Molloy and Manning-Courtney 2003); problems with sleep and the circadian rhythms are also common (Bourgeron 2007; Glickman 2010); and unusual and unpredictable pain and temperature dysregulation are well documented, particularly in autism of known etiology (Bandra et al. 2012; Dubois et al. 2010; Klintwall et al. 2011; Nader et al. 2004; Tordjman et al. 2009; Zeidan-Chulia et al. 2011). These are, however, often down-played and interpreted as “co-morbid,” secondary symptoms in the face of more obvious differences in the development of social and communicative skills. It will remain challenging to screen objectively and treat ASD based on observation and verbal reports of behaviors, particularly when the generation and control of social behaviors involve all aspects of motor control, including planning, representation, sensory-motor feedback, automatic body orienting, self-regulation, body self-autonomy, and spontaneous variability.

The disembodied, static, and centrally driven view of autism has been challenged recently by a series of studies involving various motor acts reported in >30 peer-reviewed articles in a research topic of the open-access platform, Frontiers in Integrative Neuroscience (http://www.frontiersin.org/integrative_neuroscience/researchtopics/autism_the_movement_perspective/801). In particular, studies of motor variability in ASD, posed as a stochastic process over time (Torres 2013a; Torres et al. 2013a, d), have found that the various signatures of speed-dependent variability appear to undergo a maturation process governed by a scaling power law (Torres et al. 2013a). As we typically age, the stochastic signatures of velocity-dependent parameters during pointing motions shift with age from random and noisy to predictable and reliable. However, in ASD, such transition is absent. Regardless of age, verbal capabilities, or gender, all individuals with ASD in this recent study remained within the statistical ranges of the TD 3- to 4-yr-old participants. The participants with ASD did not experience the age-dependent shifts in stochastic motor signatures that the motor patterns of TD folks manifested over time. The predictable and verifiable patterns of motor variability in our motions typically enable adequate anticipation of impending hand velocities from prior actions and can be informative of levels of intent during motor learning (Torres 2013b, c).

The recent findings in ASD invite us to think about predictable and reliable motor variability, not only as a form of motor output but also as a form of re-afferent feedback necessary for the acquisition and maintenance of a stable movement percept, anticipatory planning, and volitional control. What features(s) of this bundle of peripheral limb kinematics information may be of use to the central nervous system (CNS) in the modulation and control of our actions remain an open question. However, previous evidence from motor illusions induced by muscle-tendon vibrations has suggested that the perception of the velocity of illusory limb movements depends on the frequency and amplitude of the applied mechanical stimulation (Clark et al. 1979; Roll and Vedel 1982; Vedel and Roll 1982) and that such systematic covariances may indicate that muscle receptors, such as the dynamics-sensitive primary spindle endings, may be able to code movement velocity (Matthews 1981, 1982).

Velocity is a rich kinematic parameter that contains spatial information in its directional component and temporal information in its distance metric-dependent magnitude. These also appear to be encoded by neurons along the sensory-motor pathways of the CNS. For example, during reaching movements, several features of velocity are encoded by the primary motor cortex (Georgopoulos et al. 1986; Redish and Touretzky 1994; Schwartz 1994). However, these are also planned ahead by neurons in the reach regions of the posterior parietal cortex, as animals learn complex, curved trajectories in real time (Torres et al. 2013c). In these areas, velocity-related, ascending afferent inputs have also been reported (Prevost et al. 2009, 2010, 2011).

At the behavioral level, features related to movement velocity are often studied as averaged quantities taken over many repetitions (Shadmehr and Wise 2005). Yet, the frequency of fluctuations of velocity-dependent parameters, accumulated
continuously over time as we repeat our actions, may be a form of natural vibration that the muscular and joint afferent fibers could process, help interpret, and send as feedback to the control areas of the CNS. Several of these central areas are thought to form and anticipate a reliable motor percept (Hauschild et al. 2012; Kawato and Wolpert 1998; Mulliken et al. 2008; Wolpert et al. 1998), even in the absence of active efferent commands from ongoing movements (Torres et al. 2013c). In particular, in the parietal areas, the separation between sensory input and abstract planning has been demonstrated across several contexts (Andersen and Buneo 2002; Hwang et al. 2013; Torres et al. 2013c). Based on this prior research, we examine here velocity-dependent parameters from the continuous flow of natural, unconstrained hand motions.

We hypothesize that differences in velocity-depending variability (taken as a bundle of kinesthetic re-afferent inputs and motor outputs) may exist between ASD and controls and may be critical to differentiate further sex-based manifestations of the disorder. This hypothesis is motivated further by reported sex differences in the physiology relevant to sensory feedback from the PNS, including differences in pain-related input (Derbyshire et al. 2002; Hashmi and Davis 2009; Racine et al. 2012) and reported sex differences in smooth muscle vascular tone (Thompson and Khalil 2003), as well as sex differences in muscle fiber size and type distribution in thoracic and lumbar regions (Mannion et al. 1997).

In the present paper, we focus on the values and timing of the peak velocity during upper-limb pointing motions subject to different levels of decision-making under manipulations of the cognitive load in the visual stimuli for action. We ask if the timing information tied to the continuous flow of movements could reveal some sex differences in typical controls between deliberate and spontaneous segments of the motor decisions. We ask further whether such differences would serve to separate in any way males and females with a diagnosis of ASD.

**MATERIALS AND METHODS**

**Participants.** Seventy-eight participants (34 ASD and 44 TD), ranging from 3.5 to 61 yr of age with varying intellectual capabilities, were examined. Within the 44 TD participants, 22 were college educated, ranging from students to professors. They performed a simple biomechanical version of the pointing task (pointing to a dot) where no target-dependent decisions were included. The rest performed the pointing task and a match-to-sample version of the task where several layers of decision-making were required, according to the cognitive loads associated to the targets. The schematics of the set-up are shown in Fig. 1. Individuals with ASD had reported intelligence quotient (IQ) ranges between 40 and 110. For the TD individuals, IQ was reported as 90 and above, with education spanning from preschool to college levels. Demographic information is listed in Tables 1 and 2.

Parents signed parental consent for the children, adolescents provided assent, and adults provided their consent. The protocol was...
approved by the Institutional Review Boards of Rutgers University and Indiana University in compliance with the Declaration of Helsinki. For participants with ASD, Tables 1 and 2 report the scores from various pencil-and-paper diagnostic inventories. Licensed clinicians administered the Stanford-Binet Intelligence Scales, Fifth Edition; the ADOS (Lord et al. 2000) (communication + social scores), as well as the GARS-2 (Gilliam 2006), which confirmed the diagnosis where appropriate (e.g., for nonverbal teenage girls for whom none of the four ADOS modules currently available is appropriate).

Task and apparatus. Subjects sat comfortably in front of a computer screen. The task consisted of natural pointing motions toward a target on the computer screen (Fig. 1). All motions included the forward reach, the hand coming to rest, but as in the match-to-sample pointing version, this segment was not instructed. The continuous flow of motion was harnessed rather than only registered sample hand trajectories from this continuous flow. The hand position was controlled by a motion-caption system (Liberty, 240 Hz; Polhemus, Colchester, VT). The software developed in-house collected the screen touches and the visual-stimulus presentation, all synchronized to the same central processing unit. A computer interface logged and time stamped the presentation of the stimulus (Freeman and Ambady 2010). The software developed in-house collected the screen touches. In the simpler pointing task, subjects had to touch a dot on the screen. They then brought the hand to the target location of the monitor. The touch evoked the sample stimulus to match with one of two possible targets on the upper corners of the monitor. Upon landing the hand at the target of choice, the next trial was initiated. The participants controlled the length of the trial and the flow of the experiment. A motion-capture system (Liberty, 240 Hz; Polhemus, Colchester, VT) recorded the movements concurrently with the screen touches and the visual-stimulus presentation, all synchronized to the same central processing unit. A computer interface logged and time stamped the presentation of the stimulus (Freeman and Ambady 2010). The software developed in-house collected the screen touches. In the simpler pointing task, subjects had to touch a dot on the screen. They then brought the hand to rest, but as in the match-to-sample pointing version, this segment was not instructed.

The continuous flow of motion was harnessed rather than only registering the goal-directed, trial-by-trial segments. Figure 2A shows sample hand trajectories from this continuous flow. The hand positional trajectories were obtained, and the touches and physical plane
Biomechanical Experiment

Distributional analyses. Distributional analyses were performed on both sets of parameters. In prior work, we had discovered that the two-parameter, continuous gamma family of probability distributions captures with high confidence the continuum of human motor signatures in both typical and compromised systems (Torres 2011, 2013a, Torres et al. 2013a; Yanovich et al. 2013). Thus we used the gamma plane here to plot (shape, scale) the gamma parameters for both sets of parameters. In prior work, we had discovered that the two-parameter, continuous gamma family of probability distributions.
noisier. In the domain of motor signatures taken as re-afferent feedback, values up and to the left of the gamma plane would not provide the type of motor feedback able to accumulate evidence toward a verifiable expectation that could eventually turn into an anticipatory motor percept.

Principal component analyses of the percent of time to the maximum speed. To assess possible differences in the variability of the timing between forward and withdrawing segments of the reach across subjects, we divided the sets into TD and ASD, sorted by age.

(1) The data set was organized as an \( m \times n \) matrix, where \( m \) was the number of participants (28 girls, 44 boys) and \( n \) the number of samples/participant (50).

(2) The estimated mean was subtracted for each measurement type to center the data at zero mean.

(3) The singular value decomposition (SVD) was calculated, obtaining the eigenvectors of the covariance matrix.

(4) The principal components (PC) were plotted in matrix form for the TD and ASD groups to visualize potential differences in timing variability between the intended and unintended motions.

RESULTS

All individuals with ASD had highly skewed distributions with a tendency to slower motions and more random and noisier patterns over time (up and to the left of the gamma plane), as shown in Fig. 3B. The verbal females with ASD separated from the nonverbal females in Fig. 3D, according to the empirically estimated probability distributions for each.

Fig. 2. The navigation through the continuous flow of natural motions and the separation of goal-directed from goal-less segments of behavior. A: hand-movement trajectories from a typical child collected during 16.66 s of the match-to-sample task (240 frames/s), which required deciding between 2 stimulus choices. The blue circles mark the speed minima (pauses), whereas the black stars mark the speed maxima. The black curves denote the pointing trajectories to the green target at 2 different positions on the monitor facing the child. The blue curves are incidental to the task goal-less movements in transition to other goal-directed motions. B: corresponding speed profiles along the trajectories in A. Numbers and colors correspond to the curves in A. The speed temporal profile permits navigation through the acceleration and deceleration phases of the continuous flow of motion. C: zooming into the goal-directed speeds and D: the goal-less speed profiles that were automatically harnessed by a computer interface (see MATERIALS AND METHODS).
characterizing the female with ASD

individual when using the experimentally determined range of maximum speed values from the data set. Nonverbal and verbal females differed significantly in the dispersion of their distributions, according to the rank sum test of the individual’s Fano factor (P < 0.03 forward and P < 0.01 withdrawing movements). The dispersion in the distributions of nonverbal females with ASD was close to that of the TD individuals <4 yr old (estimated across thousands of values, P < 0.38), shown in Fig. 3C. The verbal females with ASD differed from the TD females >4 yr old (P < 0.035) and also from the TD females <4 yr old (P < 0.023). According to the estimated probability distributions, three distinct female groups appeared: TD, verbal ASD, and nonverbal ASD, thus highlighting the importance of establishing female normative data to assess atypical traits in females (rather than screening females using the male phenotype as reference, which is the current practice).

In the ASD males, <5 yr of age, no clear distinction appeared between these and the TD male children <4 yr of age in the dispersion of the empirically estimated probability distribution function (estimated across thousands of trials, forward P < 0.57; backward P < 0.87) between these and the 4- to 5-yr-old TD children (estimated across thousands of trials, forward P < 0.26; withdrawing P < 0.82). No distinctions were found between the verbal and nonverbal male participants with ASD regardless of age (estimated across thousands of values, forward P < 0.61; withdrawing P < 0.89), in contrast to the differences found between verbal and nonverbal females with ASD. The kinesthetic input that the speed-dependent variability may provide in the participants with ASD is in general noisy and lacks the diversification quantified in the TD children >4 yr old (Fig. 3, D and E).

The dispersion comparisons between the 10 females with ASD and 24 males with ASD revealed no significant differences according to the rank sum test (estimated across thousands of measurements, forward P < 0.53; withdrawing P < 0.65). It would be important to increase the number of subjects in these types of comparisons before drawing further conclusions about intergroup differences.

Overall, this velocity-dependent metric revealed marked differences in the empirically estimated probability distributions between females with ASD and TD females, even at an early age. It also revealed differences between nonverbal and verbal females with ASD that were absent when comparing verbal and nonverbal males with ASD. Furthermore, no differences appeared between the females and males with ASD regardless of age and verbal abilities, but the latter result

Fig. 3. Typical and atypical development of the statistical patterns of velocity-dependent variability. The stochastic signatures of velocity-dependent variability captured in the normalized maximum speed \( V_{max}/(V_{max} + \sigma_{V_{max}}) \) of pointing motions across different ages. The estimated shape and scale parameters of the continuous gamma probability distribution family uniquely label each individual in the group (78 participants total). A: 44 typical controls automatically cluster by age along the line of unity on the log–log gamma plane, according to a scaling power law (circles represent forward segments; diamonds represent withdrawing segments). B: 34 participants with autism spectrum disorders (ASD) also align on the line of unity. Notice that the 34 participants with ASD include verbal (V) and nonverbal (NV) subjects. They span from 4 to 25 yr of age, yet they all fall along the statistical region of the typically developing (TD) 3- to 4-yr old. C: estimated probability distributions of the velocity-dependent parameter for all typical subjects using empirically obtained hand-pointing speed ranges. Notice that the noise:signal ratio (variance/mean) changes dramatically from 3–4 to 4–5 yr of age, along with the bandwidth of parameter values that the distribution spans across subjects (significant differences, \( P < 10^{-5} \)). The 3- to 4-yr-old children all collapsed on the same curve (nondiversified mean), with the noise overpowering the signal, but the children from 4–5 yr old have acquired a verifiable kinesthetic percept with a significantly lower noise:signal ratio and a broader bandwidth of parameter values (details in RESULTS). Such diversification of the kinesthetic input is maximal in the adults who have highly reliable and predictive statistics of velocity-dependent variability, a form of kinesthetic input. D and E: the participants with ASD manifest statistical features of the 3- to 4-yr-old TD—unreliable and noisy with a narrow bandwidth of parameter values. The verbal females separate from the nonverbal females with ASD but do not quite reach the level of kinesthetic input reliability, prediction, and diversification of the 4- to 5-yr-old TD. Unlike the females, the statistical signatures of the velocity-dependent variability in the males with ASD cannot distinguish between verbal and nonverbal participants. pdf, probability density function.
should be interpreted with caution due to small subsample sizes. The most effective comparisons were between TD females and those with ASD, particularly in their (unintended) withdrawing motions, and also between TD males and those with ASD. These results strongly suggest that the sexes should be studied separately when assessing movement-based kinesthetic processing in ASD.

Normative data: typical sex differences between forward and withdrawing segments. The percent of time to reach the maximum speed differed between forward and withdrawing segments for TD females of college age but not for the corresponding males. This is shown in Fig. 4, A and B, where the points scatter about the lines, which align differently in females than in males. They have different slopes and intercepts characterizing the two sex groups. The dispersion of the empirically estimated distributions was found to be different as well. Timing was found to be more variable in the females (Fano factor ratio ranging from 0.46 to 7.28), spanning a broader range of values (reaching the speed maximum in the range $30\text{–}56\%$ of the movement duration) and unambiguously differentiating between intended and unintended motion segments (Fig. 4C). Recall here that motions aimed deliberately at the target were performed intentionally, but the retractions were uninstructed. These motions are treated differentially by the female’s sensory-motor systems compared with the male’s, a result that is very relevant in light of the objective nature of this metric. The movements of the females distinguished, on average, between the forward percent of time-to-peak velocity ($0.44 \pm 0.0023$) and withdrawing segments ($0.34 \pm 0.0063$; out of 1). In marked contrast, the males had less variability (Fano factor ranging between 0.87 and 4.83) and a narrower bandwidth of parameter ranges (reaching the maximum speed

Fig. 4. Normative, typical sex differences for a typical young adult in the percent of time to reach the speed maximum. A: the patterns of variability of the percent time to reach the maximum speed in females of college age can distinguish between forward and withdrawing segments of the reaching movements. Female forward segments can be well fit with $f(x) = mx + n; m = 0.12$, and $n = -0.71$, with 95% confidence intervals (0.026, 0.22) and ($-0.91, -0.52$), respectively, and goodness-of-fit parameters: sum squared error (SSE) = 4.7109e-006, R-square = 0.8919, root mean square error (RMSE) = 7.6737e-004. In contrast, the spontaneous retractions in the females have $m = 0.10$, and $n = -0.77$, with confidence intervals ($-0.01, 0.22$) and ($-1.00, -0.54$), respectively. The goodness-of-fit parameters were: SSE = 6.1033e-007, R-square = 0.9033, adjusted R-square = 0.8913, RMSE = 2.7621e-004. B: the males of comparable age do not have distinct patterns of variability between the forward motions intended to the target and the spontaneous withdrawing segments of the reach; $m = 0.57$, and $n = -1.07$, with 95% confidence intervals ($-1.20, -0.94$) and ($0.24, 0.91$), respectively, and SSE = 7.9535e-007, R-square = 0.9715, and RMSE = 2.8202e-004. In the withdrawing motions, $m = 0.7342$, and $n = -1.14$, with confidence intervals ($-1.26, -1.01$) and ($0.26, 1.20$), respectively, and SSE = 2.3818e-007, R-square = 0.9688, adjusted R-square = 0.9567, and RMSE = 1.5433e-004. Notice, as well, the differences in the slope and intercept of the linear-regression fit that the power relation revealed on the log–log plot of the scatter (details reported in the RESULTS). Each point of the scatter represents the empirically estimated scale and shape parameters of the 2-parameter, continuous gamma family of probability distributions of 1 subject. The empirical frequency histograms were fit using maximum likelihood estimation with 95% confidence intervals. C and D: differences in the dispersion of the distributions quantified between typical females and males of college age. Females were more variable and spanned a broader range of values, whereas males were less variable but spanned a narrower range of parameter values across the group. Each curve is the experimentally estimated gamma pdf, according to the empirically determined range of values for each person.

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at 37–40% of the movement duration) that did not distinguish the timing of the speed maxima in intended and unintended reaches as well as the females did. Forward (FWD) segments of the reach aimed at the target did not reveal differences in the PC of the variability of this (kinesthetic) latency parameter. B–D: the uninstructed retractions of the reach (backward, or withdrawing (BWD) from the target) self-segregated 2 clusters within the TD group and 1 cluster in the ASD group for each sex. Three clusters appeared for the 14 females. From rows 1–6, the younger TD females, <5 yr of age, self-aggregated and separated from the older TD females, >7 yr of age (rows 7–17). In rows 18–28, we see the variability of all of the females with ASD (4–25 yr of age), which resembles that of the TD girls <4 yr of age, even though most females with ASD were >5 yr of age. C: the PC of TD females (<5 yr of age) grouped apart from older TD females (>5 yr of age). Yet, all females with ASD had PC patterns in the range of the young TD cluster. These included verbal and nonverbal females with ASD. D: as in the young TD females, the young TD males clustered apart from the older TD males, and as with the females with ASD, the variability patterns of the timing of the maximum speed in the males with ASD grouped along the PC of the young TD. There were 2 outliers in the TD adults whose PC patterns fell on the side of the young TD (or ASD). Both were child prodigies (1 had received a diagnosis of ASD by 3 yr of age, whereas the other never received an official diagnosis). Both are presently theoretical physicists (their cases are discussed in detail in the Normative data subsection).

These differences in the statistical signatures of the variability of the maximum speed timing for TD participants led us to assess further the variability of this kinematic parameter for participants with ASD. To this end, we subtracted the mean from each measurement type to center the data at zero mean and then calculated the SVD to obtain the eigenvectors of the covariance matrix (Daffertshofer et al. 2004). The results of the PC analyses (PCA) thus performed are depicted in matrix form in Fig. 5. No apparent differences using PCA were found in the forward reaches intended to touch the target. However, in the uninstructed, withdrawing segments, marked differences were observed in the ways in which the data self-clustered, according to the PC across groups. Three clusters appeared for the females: the younger TD females, <5 yr of age, self-aggregated and separated from the older TD females, >7 yr of age; we see the variability of all of the females with ASD (4–25 yr of age), which resembles that of the TD girls <4 yr of age, even though most females with ASD were >5 yr of age. This confirmed the previous results concerning the peak velocity (Fig. 3) in the match-to-sample task between the young TD (or ASD). Both were child prodigies (1 had received a diagnosis of ASD by 3 yr of age, whereas the other never received an official diagnosis). Both are presently theoretical physicists (their cases are discussed in detail in the Normative data subsection).

Parenthetically, the PCA yielded an unexpected result. Two exceptions appeared in the TD group that clustered with the groups of participants with ASD. These two participants were child prodigies, and one of them had received a diagnosis of ASD at 3 yr of age but was considered “normal” at present.
The spontaneous motions, however, blindly situated both subjects within the ASD groups with respect to the latency of the peak velocity. This result came as a surprise, although both subjects scored very high in another study on the autism quotient questionnaire by Baron-Cohen et al. (2001). Interestingly, both subjects are, at present, theoretical physicists (as that resonates with Baron-Cohen and coworkers’ proposition that people in the resolute, exact sciences tend to have social autistic traits).

The lack of distinction between the PC in the variability of the latency of the maximum speed between TD and ASD participants for the forward reach was intriguing in light of the highly informative patterns provided by the normalized values of the maximum speed. For the females, marked differences in the dispersion of their empirically estimated distributions of the time to the maximum velocity were found between TD and ASD groups across ages (3- to 4-yr-old TD vs. low-functioning ASD, \( P < 0.03 \) rank sum test on the Fano factor; 4- to 5-yr-old TD vs. low-functioning ASD, \( P < 0.01 \); both young TD groups also differed from the high-functioning females with ASD, \( P < 0.01 \); and overall, the low- and high-functioning females with ASD differed from the young TD adults, \( P < 4.5 \times 10^{-5} \)). These differences were not observed for both forward and withdrawal motions when we compared the females with ASD and the males with ASD in both verbal and nonverbal participants (estimated across thousands of measurements, low-functioning nonverbal, \( P < 0.34 \); high-functioning verbal, \( P < 0.89 \)). There were no significant differences with respect to the dispersion of the distributions of the TD males \(< 4 \text{ yr old} \) and that of the nonverbal, low-functioning females with ASD (estimated across thousands of values, \( P < 0.17 \)), but there were differences in the dispersion between the TD males \(< 4 \text{ yr old} \) and the verbal, high-functioning females with ASD (\( P < 0.015 \)). A larger number of subjects will be needed to reassess intergroup comparisons where no significant differences in dispersion were found.

An important distinction between the latencies of the forward and withdrawal motions should be made: they were on different time scales. Forward motions were slower than the retractions (rank sum test, \( P < 10^{-5} \)). In the forward reach, the median time to the maximum speed was between 172.95 ms and 210.53 ms for those with ASD and between 109.50 ms and 179.81 ms for TD participants. In contrast, that for the withdrawal was between 93.28 ms and 108.30 ms for participants with ASD and between 60.34 ms and 152.11 ms for TD.

These results motivated us further to compare the latency of the movement DT during the match-to-sample task, which may also relate to the kinesthetic sensing of the speed timing and to the crosstalk between sensory input from vision-touch and sensory input from the unfolding motions.

**Movement DT.** With the use of the statistical self-emerging clusters obtained in Fig. 3 as a guide and those in Torres et al. (2013a), the DT frequency histograms were obtained for six clusters: three TD and three ASD.

We observed highly skewed distributions (Fig. 6) for this movement decision latency parameter, measured in seconds (Fig. 6A), with differences between clusters that were well captured by the maximum likelihood estimation (MLE) of the gamma parameters and plotted on the gamma plane, with 95% confidence intervals also plotted for each cluster in Fig. 6B. In the ASD groups, the clusters comprised nonverbal, 4- to 8-yr-old children (including males and females), with IQ \(< 50 \); nonverbal, 8- to 16-yr-old participants with IQ \(< 50 \); and verbal participants, 10–25 yr of age with IQ \( > 90 \). The TD clusters were verbal, 3- to 4-yr-old children with an estimated IQ of \( \sim 100 \); verbal children, ages 4–5, with an IQ of \( \sim 100 \); as well as college-level fellows, ages 21–30, with an IQ \( > 100 \). These subjects performed both the biomechanical pointing task and the match-to-sample task involving the pointing decisions.

We also examined the log-transformed data, which had a Gaussian tendency, to assess potential sex dependency and the effects of cognitive load. However, the log-transformed data failed the \( \chi^2 \) goodness-of-fit test for normality (\( \chi^2 = 20.11, P < 10^{-4} \)), so we used the nonparametric Kruskal-Wallis (nonparametric ANOVA) test. The groups were divided by sex to evaluate whether the DT distributions differed on this dimension. Differences between groups were found across stimulus conditions for color (\( \chi^2 = 57.16, P < 10^{-13}, 1,007 \) samples), shape (\( \chi^2 = 117.6, P < 10^{-26}, 1,199 \) samples), and rotation (\( \chi^2 = 168.06, P < 10^{-37}, 1,463 \) samples).

Further changes in the decision-making parameters reflected the motor-adaptation process that accompanied the increases in the cognitive load of the visual stimuli. Percent correct is the total percentage of correct responses for all individuals for each stimulus type. DT is the length of time from stimulus presentation to the participant touched one of the two targets. DT reduction is the average number of milliseconds by which participants got faster when comparing their performance for the first 50 trials with the last 50 trials of the task for each stimulus type. This gives a measure of performance gains over

![Fig. 6. Movement decision latency across self-emerging clusters. A: frequency histograms of the movement decision time (DT). Clusters are from self-emerging aggregates of the somatosensory, velocity-dependent kinematics parameters. IQ, intelligence quotient. B: stochastic signatures of this parameter on the (a, b) [(shape, scale), respectively] gamma plane. Note that young individuals with ASD (ages 4–8) are closer to TD individuals \( \leq 4 \) yr of age than to TD individuals \( > 4 \) yr of age, even though the latter TD group is closer in age than the former TD group.](http://jn.physiology.org/doi/10.1152/jn.00059.2013)
time. The performance of early vs. late trials was compared with assess changes in decision-making performance as impacted by the changes in motor performance as the speed profiles were adapted and changed with the cognitive stimuli from multipeaked to unimodal. The number of measurements used across stimulus types and subjects included 2,546 color, 3,588 shape, and 2,966 rotation.

The participants with ASD experienced a reduction in the movement DT between earlier and later trials, thus ruling out fatigue or boredom. Color was the stimulus type with the fastest decision [reduction of 2,285 ms, on average (2,370 ms SD)]; followed by shape [2,570.8 ms (2,926.9 ms)]; and rotation [2,739.8 ms (3,527.8 ms)]. Statistical comparison using the Kruskal-Wallis test revealed significance in ASD: $6.7 \times 10^{-7}$, $\chi^2 = 28.41$; 0.003, $\chi^2 = 11.13$; 0.05, $\chi^2 = 5.87$ for color, shape, and rotation, respectively. In the TD participants, this was also the case: $4.5 \times 10^{-5}$, $\chi^2 = 20.12 \times 10^{-5}$, $\chi^2 = 41.02$; 2.1 $\times 10^{-13}$, $\chi^2 = 58.37$, with mean ($\pm$SD) reductions (in ms) of 1,556 (1,048), 1,757 (1,480), and 2,798 (3,325) for color, shape, and rotation, respectively.

For the individual, emerging clusters, these changes were also significant across conditions for cluster 1 (nonverbal ASD, 4–6 yr old, $P < 0.0002$, $\chi^2 = 17.97$) and cluster 2 (nonverbal ASD, 8–16 yr old, $P < 5.8 \times 10^{-5}$) but not significant for cluster 3 (verbal ASD, 10–25 yr old, $P < 0.80$, $\chi^2 = 0.45$). The TD cluster 4 (kindergarten) also had a significant reduction in the latency of the decision-making motion (TD, 3–4 yr old, $P < 0.0003$, $\chi^2 = 16.53$) but not significant in the preschool cluster 5 (TD, 4–6 yr old, $P < 0.49$, $\chi^2 = 1.42$) and in the college-level cluster 6 (21–30 yr old, $P < 0.52$, $\chi^2 = 1.28$).

Tukey’s honestly significant difference post hoc tests revealed that each group was different from each other for both percentage correct and DT. The direction of significance reveals that rotation was the most difficult task (fewer correct, longer DT), whereas color was the simplest of the three tasks. $P$ values [percent correct; DT (ms)] were color vs. shape $0.0001$; 0.001; shape vs. rotation $0.05$; 0.0001; and color vs. rotation $0.0001$; 0.0001.

The MLE of the shape and scale gamma parameters is shown in Fig. 7 on the gamma parameter plane. Figure 7, A and B, compares within each male and female cluster, respectively, performance for TD vs. ASD groups. Shown are the box plots of the Kruskal-Wallis test DT (s) comparison taken across thousands of measurements, which was not significantly different for young males in Fig. 7A but was significantly different for young females shown in Fig. 7B at the 0.01 alpha level. Figure 7, C and D, compared males vs. females within each of the ASD and TD classes. Stronger differences were found between younger TD boys and girls, with a trend that changed continuously from exponential-like to skewed to Gaussian-like distributions in TD. In contrast, females with ASD showed more randomness in DT distributions with more exponential underlying distributions than males, particularly earlier in life.

These results underscore, once again, the need to examine females with ASD in relation to TD females. For all of the parameters used in our investigation, the differences were larger between TD and ASD groups within sex than between the sexes for a given group. Marked differences in variability statistics of the movement-based kinesthetic and decision-making parameters were more evident for females with ASD compared with TD females than compared with males with ASD. More importantly, these differences are quite pronounced for the youngest females with ASD that were examined.

**Decision accuracy in the match-to-sample task.** Overall, participants chose the correct target 91% of the time. Comparing accuracy between groups showed that the accuracy for the TD group was 92.4%, 86.9% for the younger ASD group, and 92% for the older ASD cohort. A Kruskal-Wallis ANOVA revealed an effect of the group on accuracy ($\chi^2 = 30.72$, $p < 0.001$, 4,976 trials). Post hoc tests revealed that the younger ASD group was less accurate than the older ASD groups ($P < 0.001$) and less accurate than the TD ($P < 0.001$) group; however, the TD group did not differ from the older ASD group. Females (93.7%) were more accurate than males (89.3%): $\chi^2 = 27.67$, $P < 0.001$, 4,976 trials.

The cognitive load of the discrimination task was partially revealed by comparing overall accuracy for the three stimulus conditions: color (95.2%), shape (94.5%), and rotation (83.4%). A Kruskal-Wallis test revealed an effect of condition-type accuracy ($\chi^2 = 175.94$, $P < 0.001$, 4,976 trials). Post hoc tests revealed that accuracy was significantly less for the rotation condition than for both the color ($P < 0.001$) and the shape condition ($P < 0.001$); however, the color and shape conditions did not differ from each other. The percent correct in the last portions of the sessions remained, here reported as mean $\pm$ SD: color ($97 \pm 18$), shape ($95 \pm 21$), and rotation ($91 \pm 29$). The variability was at its highest for rotated stimuli, and this was also the condition with the lowest accuracy.

An observation regarding accuracy of the decision-making is that the underlying statistics of the kinematics for the motion executing the decision differed dramatically between ASD and TD groups, despite overall similarities in accuracy between the two groups. Thus different mechanisms must underlie their respective accuracies. It is possible that the TD group can make better use of its predictable proprioception. Yet, in light of the noisy, narrow, and random movement-based kinesthetic input of the ASD individuals, we suggest that they may be relying on the physical, spatial properties of the visual stimuli more than on their kinesthetic sensing of velocity-dependent fluctuations to attain decision accuracy. Further research investigating this proposition is warranted.

**DISCUSSION**

In this work, possible sex differences between ASD and TD participants were investigated based on new metrics that assess movement variability over time, as manifested in the continuous flow of motions. This information is taken as a form of re-afferent proprioceptive input, partly contributed by the PNS. We also assessed differences based on the variability of decision-making parameters that may be centrally controlled. The stochastic signatures of velocity-dependent parameters, as impacted by the cognitive load of visual stimuli for decision-making, were investigated individually across a highly heterogeneous group of participants with a diagnosis of ASD and compared with TD controls. We assessed both deliberate motions toward a target and spontaneously occurring motion segments that were not instructed and that occurred largely beneath the participant’s awareness. In the pointing experiments where decision-making was also required, we measured...
the latency and accuracy of the decisions. Our hypothesis that differences in the stochastic signatures of velocity-dependent kinematics would exist in ASD and be critical to differentiate sex-based manifestations of ASD received support from the data. In particular, the data revealed normative values for TD females to be used as a basis of comparison in determining atypical traits in females. This is in contrast to current inventories that use the male phenotype as the reference for diagnosis and miss traits that are particular to the females, thus leading to the disparate diagnosis ratio of nearly five males/one female.

The velocity-dependent data showed a nontrivial statistical transition during typical development, occurring after 4 yr of age and marked by a decreased noise:signal ratio that was absent in the ASD participants. The ASD subjects never transitioned into a more reliable motor signature, one that became verifiable and diversified with age. The parameters of empirically estimated, velocity-dependent probability distributions for the participants with ASD resembled those of the TD children <4 yr of age. In the case of females with ASD, a marked distinction was found in the dispersion of their empirically estimated probability distributions that separated verbal from nonverbal participants, a pattern that we did not find in males with ASD (despite the larger sample size).

The uninstructed motions of the hand—those occurring spontaneously and below intentional awareness—were the most informative in the data. In particular, the timing of their maximum speed from segment to segment separated the ASD participants from the TD fellows. The latency of the maximum speeds of the withdrawing reaches was on the order of 30–40% of the path within a time window of 60–150 ms. These critical landmarks occurred on very short time scales in contrast to those of the forward reaches during the deliberate processing of target information (engaging vision, touch, and pressure) above 200 ms. In this regard, we propose that different GSA pathways may be mediating proprioceptive information for the types of “approach-avoidance” motions under study here. Forward motions revealing marked differ-

Fig. 7. Sex differences in the latency of the movement DT (s) across self-emerging clusters. Color codes are as before (green, TD <4 yr old; blue, TD >4 yr old; red, TD college level; magenta, nonverbal ASD 4–6 yr old; maize, nonverbal ASD 8–16 yr old; black, verbal ASD 10–15 yr old). A: male participants overall show significant differences between ASD and TD (Kruskal-Wallis, \( P < 1.02 \times 10^{-7}, \chi^2 = 28.32 \)). B: the differences between females with ASD and TD are also significant (Kruskal-Wallis, \( P < 0.004, \chi^2 = 8.25 \)), yet they were more pronounced in the younger girls, around the ages of 3–4 (TD) vs. 4–5 (ASD). By then, the differences in movement decision latency are significant in females (Kruskal-Wallis, \( P < 1.10 \times 10^{-16}, \chi^2 = 68.78 \)) but not in males (Kruskal-Wallis, \( P < 0.32, \chi^2 = 1.01 \)). Black arrows highlight the separation between males (A) and females (B) in the clusters of TD kindergarten (green) and 4- to 6-yr-old nonverbal participants with ASD. C: males and females with ASD showed significant differences across ages (Kruskal-Wallis, \( P < 4.30 \times 10^{-9}, \chi^2 = 34.47 \); Kruskal-Wallis, \( P < 1.00 \times 10^{-14}, \chi^2 = 59.87 \); Kruskal-Wallis, \( P < 5.60 \times 10^{-5}, \chi^2 = 16.23 \)). D: TD males and females showed significant differences at the kindergarten (Kruskal-Wallis, \( P < 0.0009, \chi^2 = 10.98 \)) and preschool (Kruskal-Wallis, \( P < 0.0004, \chi^2 = 12.37 \)) levels, but these were not significant at the college level (Kruskal-Wallis, \( P < 0.16, \chi^2 = 2.0 \)).
ences in the statistics of intended speed values may be routed through GSA pathways that reach somatosensory cortex via the thalamus (O’Rahilly and Müller 1983). The withdrawal of motions incidental to the task and automatically occurring at significantly shorter time scales, largely beneath intentional awareness, may be routed through phylogenetically older pathways to the cerebellum and other older, central subcortical structures comprising the limbic system and the striatum.

It is possible that the early developmental glitch that leads to autism in each individual disrupts first the more primitive systems—those that appeared first in evolution. Adaptive compensatory mechanisms may then change the typical development of proper feedback loops toward and within the central commanding areas of the neocortex and result in different coping control mechanisms. Such coping strategies would allow the system to survive but would impede the balance between voluntary and automatic control of behavior. This would result in poor body autonomy and self-regulation, which in turn, would impede volitional control. We are, at present, testing these ideas in the context of new therapeutic concepts for ASD.

Evidence in support of these ideas comes from various disconnected sources of research that need to be integrated. In idiopathic autism, older, central core structures of the brain are known to be disrupted. These include the amygdala, striatum, and cerebellum (Amaral et al. 2008; Courchesne 1991, 1997; Mostofsky et al. 2009; Nayate et al. 2005; Schumann et al. 2004). In some forms of autism of known etiology, GSA pathways conducting movement, pressure, pain, and temperature information are also known to differ by virtue of dysfunctional proteins that are essential for postsynaptic scaffolding [e.g., SHANK 3 in Phelan-McDermid syndrome (Phelan and Rogers 1993)]. Such disruptions give rise to stochastic motor patterns similar to those seen in this report (Torres et al. 2013b). Some manifestations of the phenotype are high tolerance to pain, temperature dysregulation, lack of fear, and lack of a general sense or awareness of body in space and time. These individuals also go on to receive a diagnosis of ASD, because such afferent anomalies disrupt social and communicative abilities (Aldinger et al. 2013; Phelan and McDermid 2012; Phelan and Rogers 1993; Phelan 2008; Phelan et al. 2001; Strenge et al. 2008; Uchino and Waga 2013). Reports from parents, self-advocates, and neurologists about individuals with idiopathic autism describe symptoms that concord with the phenomenology of this syndrome of known etiology (Damasio and Maurer 1978; Donnellan and Leary 1995; Maurer and Damasio 1982; Robledo et al. 2012). This suggests that, at least in part, the noisy and random motor patterns uncovered here may contribute to noisy re-afferent feedback. However, further research will be necessary to establish definitely the origins of such general patterns in ASD and to separate the motor from the sensory components in the velocity-dependent signal.

Given the present sex differences in movement parameters and the finding that these differences manifest maximally when females are compared with normative female data, it will be important to examine systematically the physiology of peripheral and subcortical areas involved in the feedback loops for proper motor control so as to determine possible physiological sex differences that would explain those unveiled here in the motor readout. In this regard, several mouse models have been created yielding phenotypes that involve social impairments similar to autistic-like symptoms (El-Kordi et al. 2012; Giza et al. 2010; Jamain et al. 2003, 2008; Peca et al. 2011; Tabuchi et al. 2007; Wang et al. 2011), yet no objective measurements of their behavior have been provided beyond descriptive observations. Given that motor variability is also present in the animal behaviors, our framework offers a new avenue for objective quantification of sex differences in the physiology of motor control using animal models of ASD.

It will be important in our future research at the behavioral level to disentangle and refine further the statistical differences in movement variability that we have found between different functional classes of movements, particularly with respect to differing manifestations of these in males and females with ASD. The phylogenetically different GSA pathways may hold promise in shedding light on the much-needed characterization of the phenotype of females with ASD, because evolution endowed males and females with different endocrine systems bound to impact differently the somatosensory capacities and their maturation rates. The autistic system, as any biological system, has adaptive capabilities and changes over time. One of the advantages of the present metrics is that they enable the individualized dynamic tracking in real time of the nonstationary statistics of natural movements as a function of age and developmental stage. Thus we could track the same individual longitudinally and chart out the developmental trajectory of the stochastic signatures of his/her motor readout of some aspects of internal proprioception (Torres et al. 2013a).

In tandem with the kinesthetic-related parameters, decision-making parameters, such as the latency and the accuracy of the decision, were also examined here. These analyses revealed marked differences between males and females with ASD. Importantly, as with the kinematics data, the differences were more remarkable when examining females with ASD relative to TD females. This trend was more pronounced for younger subjects (even within a small sample size), yet the differences also manifested in the older females with ASD. Our results may be important in light of the present inventories that lack provisions to characterize the female phenotype and rather use the male phenotype as the reference. The most important finding of this study is precisely the revelation that normative data are different between TD males and TD females and that when looked at relative to this normative data, the youngest females with ASD in the group are maximally different.

Conclusion and future steps. Although disturbances in movement proprioception are not part of the core symptoms that define ASD and although most research focuses on centrally based intentionality, planning, and subjective inferences, it may be worthwhile to turn our attention to the body physiology in ASD and to the potential contributions of afferent peripheral inputs from the somatic, autonomic, and enteric nervous systems to the formation of mental operations involved in social exchange.

The present results on sex-based differences in the statistics of velocity-dependent motor patterns invite further examination of the movement variability of individuals with ASD in relation to TD controls. We suggest that the patterns uncovered here may reveal marked developmental differences in re-afferent kinesthetic sensing between individuals with ASD and controls. To test this proposition in future work, it will be important to separate potential contributions to action planning.
and control by re-afferent sensory prediction from contributions by the efference copy of ongoing, centrally driven motor commands. Both components of internal models for action may be disrupted in ASD, where reports of low muscle tone, high tolerance to pain, and temperature dysregulation abound. These anomalies may also contribute to their lack of body awareness, emotional dysregulation, and lack of volitional control of actions on command. In this regard, it has been our finding that in ASD, spontaneous motions occurring largely beneath awareness have patterns of variability closer to those quantified in typical controls (Torres 2013a; Torres et al. 2013a, d). However, the stochastic signatures of peak velocity and acceleration from intentional segments of the reach in our participants with ASD (both verbal and nonverbal) align well with the patterns of deliberate pointing from a patient without proprioception (Torres et al. 2012), thus suggesting that at least in part, corrupted proprioception may underlie some of the anomalies in volitional control. There have been previous reports of no proprioceptive deficits in high-functioning verbal individuals with ASD (Fuentes et al. 2011; Haswell et al. 2009; Izawa et al. 2012), but studies of nonverbal, so called “low-functioning” individuals have been lacking. In particular, those involving analyses of kinematics in verbal and nonverbal females with ASD were nonexistent.

We have been able to use in children with ASD the spontaneous variability present in natural behaviors to evoke and sustain intentionality in their actions, so as to shift their random and noisy motor patterns into predictable and reliable regimes (Torres et al. 2013d). The spontaneous self-discovery of cause-effect by these individuals, in the absence of explicit instructions, has helped them connect their intentions to their actions and retain positive gains over time. These gains and retention are absent in other therapeutic interventions (Black et al. 1972; Cooper et al. 1987) that explicitly command the individual under the hidden assumptions that top-down regulation in ASD exists (from neocortex to subcortical to peripheral pathways) and develops, as in the typical participants. TD participants can follow command, have body self-autonomy, and self-regulate. In ASD, none of these basic functions is typical. We have proposed that new interventions in autism, where the peripheral input is used to evoke central control in a bottom-up fashion (from peripheral to subcortical to neocortical regions), will be more appropriate than approaches that assume that top-down control is intact in ASD. The autistic system may have developed different adaptive-coping strategies to compensate for the lack of or the corrupted motor feedback (Brincker and Torres 2013; Torres et al. 2013a, d). In light of the present results on sex specificity, we plan to tailor such therapies to female and male sensory-motor timing features.

Because of the atypical developmental trajectories of their motion patterns and the lack of age transition into more predictive, reliable, and anticipatory patterns, it may be possible that central (cortical/subcortical-based) control differs in ASD. Perhaps recruiting the PNS in ASD and guiding it through more primitive subcortical mechanisms, particularly those involved in affective and emotional regulation, tempo, rhythm, etc., would lead to better focus, self-regulation, and eventually, intentional control. Taking this “back-door” route in neurological music therapies (Hardy and LaGasse 2013) has helped children find autonomy and self-regulate, as suggested also by metronome-based interventions and interventions that involve the acquisition by low-functioning, nonverbal individuals with ASD of independent typing and communication abilities through emotional support (Dowden and Marriner 1995; Kasa-Hendrickson et al. 2009; Orleivsky and Curkier 2013). Timing and rhythms seem to be critical to connect with the individual with ASD (Amos 2013; Barnhill 2013). Here, the sex differences may help refine such therapeutic interventions and tailor them to harness the capabilities and predispositions of each individual in the spectrum.

Differences in timing variability, objectively quantified here in decision-making processes that occurred in tandem with the hand motions, were also uncovered in the uninstructed motions, performed largely below intentional awareness. These types of motions will open a window into the potential capabilities of nonverbal individuals with ASD, currently, largely under studied. Spontaneous acts do not require verbal instructions or their understanding by the participant. Our metrics can also quantify such motions. Overall, the differences in decision-making parameters revealed precise sex differences. The new framework and simple experimental paradigms that we introduce here could be useful in the near future to aid researchers and clinicians in the tracking of the continuous flow of natural behaviors (Torres 2013b, c; Torres et al. 2013d). They could easily and systematically reproduce our results by testing them within each sex group of the general population and begin strategizing to find the path toward the objective characterization of the female phenotype with ASD.

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DISCLOSURES

There is no conflict of interest from any of the authors.

AUTHOR CONTRIBUTIONS


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